PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/003150	21.07.2004	30.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07K7/06, A61K51/08, A61K47/48, A61K49/00

Applicant
AMERSHAM HEALTH AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/003150

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9 (for IA)

because:

☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. -

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	1-14
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-8,10-14
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/003150

Re Item I
Basis of the report

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: WO 03/006491 A (INDREVOLL BAARD ; SOLBAKKEN MAGNE (NO); AMERSHAM HEALTH AS (NO); CUTHB) 23 January 2003 (2003-01-23)
   D2: WO 01/77145 A (INDREVOLL BAARD ; CUTHBERTSON ALAN (NO); NYCOMED IMAGING AS (NO)) 18 October 2001 (2001-10-18)
   D3: WO 02/062819 A (BONASERA THOMAS A ; LIVNAH NURIT (IL); PEPTOR LTD (IL); SALITRA YOSEPH) 15 August 2002 (2002-08-15)
   D4: US-A-5 888 474 (LISTER-JAMES JOHN ET AL) 30 March 1999 (1999-03-30)
   D5: WO 02/20610 A (SRINIVASAN ANANTHACHARI ; ERION JACK L (US); MALLINCKRODT INC (US); SC) 14 March 2002 (2002-03-14)
   D6: PEARSON D A ET AL: "THROMBUS IMAGING USING TECHNETIUM-99M-LABELED HIGH-POTENCY GPIIB/IIIA RECEPTOR ANTAGONISTS. CHEMISTRY AND INITIAL BIOLOGICAL STUDIES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 7, 1996, pages 1372-1382, XP002061485

ISSN: 0022-2623

D7: HARRIS T D ET AL: "Tc-99m-labeled fibrinogen receptor antagonists: design and synthesis of cyclic RGD peptides for the detection of thrombi" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 15, 6 August 1996 (1996-08-06), pages 1741-1746, XP004135594 ISSN: 0960-894X

2. *Novelty and Inventive Step (Article 33(2)(3) PCT)*

2.1 The present application addresses bicyclic peptides having the amino acid sequence KCRGDCFC being substituted at the C-terminus with a PEGylated moiety, at the ε-amino group with an antineoplastic agent, a chelating agent or a reporter group bound via a linker molecule of the PEG-type. The C-terminal cysteine sulfur is bound as thioether via a methylene carbonyl group to the N-terminus. The other cysteines are bridged via a S-$(CH_2)_{1-4}$-S link. These compounds are also claimed as being used in radiopharmaceutical compositions, a method for *in vivo* diagnosis. A method of preparation is claimed too.

2.2 D1, which considered representing the closest prior art, discloses compounds which differ only in the lack of the methylene groups between the sulfur atoms of the Cys-Cys bridge. The other prior art documents are more remote concerning the amino acid sequence as well as the nature of the bridges forming the cyclic peptides.
The subject-matter of present claims 1-14 is therefore novel.

Taking the disclosure of D1 into consideration, the problem underlying the present application is to be regarded as to provide further alternative bicyclic peptides which can act as targeting compounds in diagnosis and therapy of diseases related to VEGF, i.e. to neovascularisation, thereby being chemically robust against attacks to the bicyclic structure which stabilises the particular conformation (see also pages 5 to 6 of D1).

The solution presented by the present application is the introduction of a methylene group linking the Cys sulfurs. This solution is not suggested by the closest prior art alone or in combination with any of the prior art documents D2 to D7. D3 discusses the influence of the ring size upon the activity of backbone cyclised radiolabelled somatostatin analogues but mentions explicitly that bridges

involving side chains of the amino acids should be avoided in order to prevent negative effects on the ligand binding to the receptor. The teaching of this document leads the skilled person away from the proposed solution. The other documents do not even deal with the problem of the stability of conformationally constrained bicyclic peptides. The subject-matter of present claims 14 is thus considered involving an inventive step.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 is not mentioned in the description, nor are these documents identified therein.

2. The attention of the applicant is drawn to the following:
The use of the expression "...*incorporated by reference*..." (see page 17, line 13 of the description) is not allowed in some designated Contracting States. When entering the Regional/National phase these expressions should be deleted from the application.